UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,632	06/09/2000	Susan Lindquist	27373/34978A	2820

7590 07/30/2002

Marshall O'Toole Gerstein
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6402

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/30/2002 15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/591,632	Applicant(s) Lindquist et al.
	Examiner Michael Brannock, Ph.D	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 13, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *see attached* is/are pending in the applica

4a) Of the above, claim(s) *see attached* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *see attached* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 10
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 1, 2, 4, 7, 19, 20, 22, 24-32, 46, 48, 55-58, 60, 61, 63, 66, 97, 111-114 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14, 5/13/02.

Applicant's election with traverse of Group V, claims 65, 67, 81, 101-110, 115-118 drawn to polypeptides having a reactive SCHAG amino acid sequence, a modified cysteine residue, and a metal atom substituent, in Paper 14 is acknowledged. It is noted that the restriction requirement inadvertently included claim 66 in Group V, however this is an obvious clerical error because claim 66 is directed to polynucleotides encoding a reactive SCHAG sequence which is clearly encompassed by Group VI and not Group V. Applicant appears to allege that the polypeptides of Group V can only be prepared using the polynucleotides of Group IV, i.e., Applicant argues that the examiner alleges that the materials of Group V can be isolated or purified from natural sources but in fact a modification requiring substitution of a reactive group is recited in the claims. This argument has been fully considered but not deemed persuasive. The examiner indicated that the products encompassed by the claims of Group V "can be prepared by processes which are materially different from recombinant DNA expression of Groups I and VI, such as by chemical synthesis, or by isolation and purification from natural sources". Thus, the restriction requirement clearly indicates, as is old in the art, that amino acid

substitution, as required by the claims, can be effected through chemical synthesis of the polypeptide. Further, Applicant's arguments appear to directly contradict the instant specification wherein it is specifically stated that reactive SCHAG polypeptides having amino sequence substitutions can be constructed using peptide synthesis, see page 25, lines 18 and 19.

Applicant argues that examination of Group IV with elected Group V would not create a search burden because a search of one group would likely share common attributes with a search of the other. This argument has been fully considered but not deemed persuasive. Although a search of any one of the groups may overlap that of another, the search of one group could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of any other group, and to search all groups would be burdensome.

Applicant argues that the restriction requirement has failed to articulate a recognized basis for restricting Group IV from Groups V and VI. Applicant's attention is drawn to the second paragraph of page 4 of the restriction requirement wherein the following is recited "The polynucleotides of Groups I and IV are related to the methods of Groups III and IV as product and process of use." This sentence contains an obvious typographic error because Group IV is not directed to polynucleotides and would also not be separated from itself as the sentence literally reads. It is the polynucleotides of group VI and not IV that the sentence is referring to. The sentence should read "The polynucleotides of Groups I and VI are related to the methods of Groups III and IV as product and process of use". Additionally, in the first paragraph of page 5

the restriction requirement sets forth that the polypeptides of Group V are patentably distinct from the methods of Group IV because one is not required for the use of the other.

Applicant additionally argues that the election of a substituent with respect to Group V is inappropriate in so far as the generic claims do not require a substituent. This argument has been fully considered but not deemed persuasive because the claims specifically contemplate substituents as obviated by dependent claim 109. Therefore, the restriction is deemed to be proper; it is maintained and made final.

Claim Rejections - 35 USC § 112

2.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 117 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require an amino acid sequence of SEQ ID NO: 1, yet the sequence listing indicates that SEQ ID NO: 1 is a nucleic acid sequence. It appears that the claims were intended to recite "SEQ ID NO: 2" and not "SEQ ID NO: 1"; claims so amended would be allowable.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 65, 67, 101, 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Gregori et al., J. Biol. Chem. 272:1(58(62)1997.

Gregori et al. disclose a polypeptide comprising a self-aggregation domain of Amyloid-β protein (residues 1-40, as is well known in the art) comprising the substitution of residue 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold), see col 1 of page 59. Gregori et al. further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill in the art would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because the gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate.

6. Claims 81 and 115 are rejected under 35 U.S.C. 102(b) as being anticipated by Paushkin et al., Science 277(381-383)1997. The specification asserts that cysteine, lysine, tyrosine, glutamate, aspartate, and arginine possess reactable side chains (e.g. page 24) and that the NM

fragment of yeast Sup35p has multiple cysteine, lysine, tyrosine, glutamate, aspartate, and/or arginine residues wherein the side chains are exposed to the environment and could serve as reactive sites in ordered aggregates of the polypeptide, see Table at page 86 for example. Paushkin et al., disclose the NM fragment of yeast Sup35p, see Fig. 1, for example.

7. Claims 65, 67, 81, 101, 115 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/28471.

WO 96/28471 disclose polypeptides and aggregates thereof produced in a method of making a polypeptide comprising identifying a SCHAG amino acid sequence (i.e. an amyloid aggregation core domain (ACD), see page 4, line 2) capable of forming ordered aggregates (page 10, lines 19-32), wherein the polypeptide may have one or more reactable amino acid side-chain substitutions (e.g. pages 23-25), such that the reactable amino acid side-chain substitution can be modified with a detectable substance, e.g. fluorescein-containing groups or metal ions, e.g. technetium pg 24 and 29, such side chain modifications being assayed to determine if the side chain is exposed to the environment during aggregate formation, i.e. determining that the substitution is useful for detecting the aggregate and/or does not inhibit aggregation would indicate that the side chain is exposed to the environment (pg 17, last paragraph and pg 29 last paragraph). Further, WO 96/28471 teaches the modification of two different selectively reactable side chains, see page 24).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 102-110 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over King et al. PNAS 94(6618-6622)1997 in view of Gregori et al., J. Biol. Chem. 272:1(58(62)1997.

King et al. teach that residues 2-114 of the yeast Sup35 protein constitute the prion aggregation domain (see the Title and Abstract) see the Abstract and page 6618 and col 2 of page 6621. King et al. also teach the use of a polyhistidine tag (page 6618) to purify the protein, as is old in the art. Further, the use of polyhistidine tags or epitope tags for protein purification is old and established in the art. King et al. teach methods of monitoring the ordered aggregation of prion-like proteins, e.g. Electron Microscopy, Circular Dichroism, Protease K resistance assay and seeding assay (see Experimental Procedures). King et al. do not disclose that the method of monitoring aggregate formation involve the use of a gold labeled polypeptide, wherein an amino acid exposed to the environment is substituted with an amino acid having a reactable side chain.

Gregori et al. disclose an improved method of monitoring prion-like aggregation with electron microscopy using a gold labeled substituted amino acid (see the Abstract). Gregori et al. disclose a polypeptide comprising a self-aggregation domain of Amyloid-β protein (residues 1-40) comprising the substitution of residue 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold), see col 1 of page 59. Gregori et al. further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill in the art would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because the gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate.

Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success, at the time the invention was made, to substitute an amino acid bearing a side chain exposed to the environment (i.e. an amino acid wherein substitution of which would not disrupt aggregate formation) with a lysine residue and to label the lysine residue with a gold ion for use in electron microscopic investigation of prion-like aggregate formation as taught by Gregori et al. when practicing the method of monitoring the prion-like aggregate formation of the Sup35 protein as taught by King et al.. The motivation to do so is provided by King et al. who demonstrate the importance of monitoring prion-like aggregate formation of the Sup35 protein.

10. Claims 65, 67, 81, 101, and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5750361 in view of Stayton et al. J. Biol. Chem. 263(27)1344-13548, 1988.

U.S. Patent No: 5750361 discloses methods of assaying formation of prion complexes (i.e. SCHAG amino acid sequences) by constructing polypeptides comprising prion aggregation domains labeled using materials and methods well known in the art including florescent dye and spectrophotometrically-detectable chromophores (see col 11 bridging col 12). U.S. Patent No: 5750361 discloses assays to determine that the labeling occurs at positions exposed to the environment, i.e. that the label does not interfere with complex formation (e.g col 11 and 12). U.S. Patent No: 5750361 does not specifically recite that the act of labeling the polypeptide include the steps of choosing an amino acid residue in the sequence having a side chain that is exposed to the environment and substituting this amino acid with one having a reactive side chain; however these steps are old and well established to in the art of protein complex detection. For example, Stayton et al. disclose a method of labeling a polypeptide comprising identifying a residues having a side chain exposed to the environment (Threonine at positions 6 and 68 of Cytochrome b5) and substituting these residues with residues having a reactive side-chain and further modifying the reactive side chains with a fluorescent agent (see the Abstract and col 2 of page 13544). U.S. Patent No: 5750361 also disclose that the polypeptides can be further modified to accept a biotin group through methods well known in the art, e.g. derivation of a reactive lysine side chain (see col 12, L27-39).

Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain for use in an assay to detect prion aggregates (and thus producing the aggregates themselves) labeled with a fluorescent or other spectrophotometrically-detectable substituent, and also a lysine residue for biotinylation, as taught by U.S. Patent No: 5750361 and to accomplish this by selecting a residue having a side chain exposed to the environment and replacing that residue with one having a reactable side chain and then further modifying the side chain with a fluorescent dye, as taught by Stayton et al. and/or a biotin molecule as is old in the art. The motivation to do so was provided by U.S. Patent No: 5750361 wherein it is stated that the polypeptide should be modified as described in the art and that amino acids could be substituted as long as the change does not effect complex formation (col 7, L30-36) and by Stayton et al who provide methods of labeling a polypeptide, wherein the labeled polypeptide is useful for detection of complex formation.

11. Claims 102-109 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5750361 in view of Stayton et al. J. Biol. Chem. 263(27)1344-13548, 1988 and in further view of King et al. PNAS 94(6618-6622)1997.

Claims 102-109 and 116 require the elements of claims 65, 67, 81, 101, and 115, as discussed above, yet claims 102-109 and 116 also require the aggregation domain be that comprising residues 2-113 of the yeast Sup35p and also a epitope or poly histidine tag. King et

al. that residues 2-114 of the yeast Sup35 protein constitute the prion aggregation domain (see the Title and Abstract) and are analogous to the amyloid aggregation domains (referred to in the U.S. Patent No: 5750361), see the Abstract and page 6618 and col 2 of page 6621, as is well established in the art. King et al. also teach the use of a polyhistidine tag (page 6618) to purify the protein, as is old in the art. Further, the use of polyhistidine tags or epitope tags for protein purification is old and established in the art. U.S. Patent No: 5750361 further teach the use of epitopes (i.e. epitope tags) to monitor the aggregate forming properties of the polypeptides (see col 9, L52 to col 10, L12).

Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain comprising residues 2-113 the yeast Sup35p, as taught by King et al. for use in an assay to detect prion aggregates as taught by both U.S. Patent No: 5750361 and by, King et al, labeled with a fluorescent or other spectrophotometrically-detectable substituent, and also a lysine residue for biotinylation, as taught by Stayton et al., wherein the reactive side chains are introduced by amino acid substitution as taught by Stayton et al. It would also be obvious to further monitor the aggregation of the polypeptides using epitope tags, as taught by Stayton et al. The motivation to do so was provided by both King et al. and U.S. Patent No: 5750361 wherein the importance of monitoring the prion-like aggregation of polypeptides is particularly pointed out (see the Abstracts of both King et al. and U.S. Patent No: 5750361).

Conclusion

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

July 25, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600